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ORIGINAL ARTICLE

Model to predict survival after surgical resection of intrahepatic cholangiocarcinoma: the Mayo Clinic experience

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Abstract

Background: The 7th edition of the American Joint Committee on Cancer (AJCC) staging system has recently been validated and shown to predict survival in patients with intrahepatic cholangiocarcinoma (ICC). The present study attempted to investigate the validity of these findings.

Methods: A single-centre, retrospective cohort study was conducted. Histopathological restaging of disease subsequent to primary surgical resection was carried out in all consecutive ICC patients. Overall survival was compared using Kaplan–Meier estimates and log-rank tests.

Results: A total of 150 patients underwent surgery, 126 (84%) of whom met the present study's inclusion criteria. Of these 126 patients, 68 (54%) were female. The median length of follow-up was 4.5 years. The median patient age was 58 years (range: 24–79 years). Median body mass index was 27 kg/m^2 (range: 17–46 kg/m^2). Staging according to the AJCC 7th edition categorized 33 (26%) patients with stage I disease, 27 (21%) with stage II disease, five (4%) with stage III disease, and 61 (48%) with stage IVa disease. The AJCC 7th edition failed to accurately stratify survival in the current cohort; analysis revealed significantly worse survival in those with microvascular invasion, tumour size of >5 cm, grade 4 disease, multiple tumours and positive lymph nodes ($P < 0.001$). A negative resection margin was associated with improved survival ($P < 0.001$).

Conclusions: The AJCC 7th edition did not accurately predict survival in patients with ICC. A multivariable model including tumour size and differentiation in addition to the criteria used in the AJCC 7th edition may offer a more accurate method of predicting survival in patients with ICC.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is a malignant neoplasm originating from the epitheliocytes of bile ductules.[1] It is the second most common primary malignancy of the liver and has reported incidences of 0.5–2.0 per 100 000 individuals in the adult population of the USA.[2,3] Recent studies suggest its incidence is rising worldwide.[4] Surgery continues to be the only modality shown to prolong survival.[5–7] One- and 5-year survival rates in those with unresectable disease are reported to be 23% and 3%, respectively.[8,9] However, post-resection overall survival rates of 70–80% at 1 year[7,8] and 30–35% at 5 years[7,10] have been reported.

Correct staging to accurately identify patients who would benefit from major surgical resection is critical to the appropriate management of these patients. The introduction of unique staging for ICC in the 7th edition of the American Joint Committee on Cancer (AJCC) cancer staging system[11] was a major step towards providing exclusive prognostication in Western populations. The main differences with the 6th edition of the AJCC staging system were the removal of tumour size from the staging and the inclusion of tumour features such as periductal invasion, vascular invasion and tumour multiplicity. The staging system proposed was found to be superior to the staging systems suggested by

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Yamasaki[12] and Okabayashi *et al.*[13] in its ability to discriminate for survival utilizing patients in the Surveillance, Epidemiology and End Results (SEER) database.[14] However, the utilization of such an outcomes database entailed considerable gaps in data and incomplete clinical information, including that on tumour–node–metastasis (TNM) staging (pNx was considered pN0), incomplete T-staging in some N0M0 patients (63 patients with pTx with poor survival), and missing information on resection status and tumour growth type.[15] Recently, two multicentre studies[16,17] originating from Europe tried to evaluate the validity of this current staging system in independent population datasets with equivocal results.

The primary aim of the current study was to report a single-centre, large-volume experience of survival outcomes in patients with ICC submitted to primary curative surgical resection. The secondary aim was to examine whether or not the 7th edition of the AJCC staging system accurately predicted survival in such a cohort.

Materials and methods

Patients

The study was approved by the Mayo Clinic's Institutional Review Board. Subsequently, all consecutive patients with ICC who were treated with primary surgical resection between 1997 and 2011 at the Mayo Clinic (Rochester, MN, USA) were identified. Patients with evidence of M1 disease and patients treated with palliative operations were excluded. A prospective histopathological re-review of slides was performed by one pathologist (TM). Data for patients for whom slides were not available for review were excluded from the analysis.

Clinicopathological variables of interest

Demographic covariates included age, gender, race and body mass index (BMI) (kg/m^2). Histopathological covariates included tumour growth type, grade, necrosis, invasion (microvascular, macrovascular and neighbouring organs), multicentricity, hepatic steatosis or fibrosis, primary sclerosing cholangitis, haemochromatosis, cirrhosis and lymph node status. Liver resections were categorized as major when four or more liver segments were resected. Vascular resection was categorized as major when the inferior vena cava or portal vein was reconstructed. The AJCC staging system (7th edition)[11] was used to categorize the T-stage and N-stage, and to provide overall staging. In addition, the resection margin was categorized as negative (R0) when the tumour was not at the inked margin, or as microscopically positive (R1) or macroscopically positive (R2). Only patients submitted to lymph node excision were included in the study. Lymph node excisions included the regional sampling of lymph nodes and lymph node dissection. Lymph node dissection was defined as the formal removal of the hilar, periduodenal and peripancreatic lymph nodes in the right liver and the removal of the hilar and gastrohepatic nodes in the left liver. The presence of any positive lymph node was considered to indicate pN1 disease. Overall survival was calculated as the time from operative resection to the date of the patient's death from any cause or last follow-up visit, at which point data were censored.

Histopathological examination

All resected specimens were subjected to gross and microscopic pathological examination. Gross evaluation of tumours included the measurement of tumour size, count of tumour masses, assessment for gross vascular invasion (gross involvement of large vessels), gross evaluation of the resection margin, and measurement of the distance between the tumour mass and the resection margin. The tumour growth pattern was classified as being of mass-forming type, periductal infiltrating type, or intraductal and mixed mass-forming/periductal infiltrating type, according to the AJCC guidelines.[11] Patients with periductal infiltrating type, intraductal and mixed mass-forming/periductal infiltrating type were combined and classified as 'other' because the sample size was small. All specimens were diligently dissected to search for lymph nodes; all lymph nodes were submitted to microscopic examination. Microscopic examination of all specimens was performed by a single hepatobiliary pathologist (TM). This included the evaluation of the submitted haematoxylin and eosin-stained sections of both the tumour mass and background liver parenchyma. Tumours were graded according to the four-tier quantitative grading system adopted by the College of American Pathologists (CAP).[18] Instances of grade 3 and grade 4 disease were grouped together as 'high grade'. The total number of lymph nodes removed and the total number of lymph nodes positive for metastatic cholangiocarcinoma were recorded.

The background liver parenchyma was evaluated for fibrosis, steatosis or steatohepatitis, haemosiderosis, and primary sclerosing cholangitis by standard pathological examination techniques.[19,20]

Statistical analysis

Statistical analyses were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC, USA). Descriptive statistics were reported for all study variables as the median with range or as the count with percentage as appropriate. Survival was estimated for patients according to the AJCC 7th edition classification using the Kaplan–Meier method. Similarly, estimates were made for patient variables, tumour characteristics in addition to AJCC stage, and surgical variables. A Cox proportional hazards model was used to assess the association of AJCC 7th edition stage with patient survival and the concordance index for the model was reported. A multiple-variable model utilizing patient characteristics was used to assess survival; another model utilized only tumour characteristics, and a third used surgical variables. Finally, a single multiple-variable model was used in the three separate models. Random forest plots were utilized in the selection of multiple-variable models in addition to the usual variable selection methods (backward and forward). The final single multiple-variable model was run incorporating the same variables and in addition the AJCC

Table 1 Patient demographics, tumour features and liver resection data in 126 patients with intrahepatic cholangiocarcinoma

Demographics	
Length of follow-up, median (range)	4.5 years (5 days to 14 years)
Age, years, median (range)	58 (24–79)
Gender, female, *n* (%)	68 (54%)
Body mass index, kg/m^2, median (range)	27 (17–46)
Cirrhosis, *n* (%)	9 (7%)
Primary sclerosing cholangitis, *n* (%)	5 (4%)
Haemochromatosis, *n* (%)	2 (2%)
Tumour features and liver resection	
Tumour size, cm, median (range)	7.0 (0.7–20.0)
Growth type, *n* (%)	
Mass-forming	83 (66%)
Other (periductal, intraductal and combined)	43 (34%)
High grade (grades 3 and 4)	68 (54%)
Multiple tumours	44 (35%)
Invasion, *n* (%)	
Macrovascular	11 (9%)
Microvascular	65 (52%)
Periductal	41 (33%)
Perineural	46 (37%)
Direct invasion	11 (9%)
Fibrosis	49 (39%)
Steatosis	19 (15%)
Major liver resection, *n* (%)	56 (44%)
Major vascular resection, *n* (%)	14 (11%)

7th edition variable. The concordance index (defined as the generalization of the area under the curve and as measuring the predictive ability of a model) was calculated for the models and various staging systems and reported along with 95% confidence intervals (CIs). An α-level of 0.050 was considered to indicate statistical significance.

Results

A total of 150 patients underwent surgical resection for ICC during the study period. A total of 24 patients (16%) did not undergo lymph node evaluation and their data were excluded from the analysis. Demographics, tumour features and surgical interventions are shown in Table 1.

An R0 resection margin was achieved in 110 (87%) patients; the median margin width was 4 mm (range: 1–45 mm). Lymph node dissection was performed in 46 (37%) of the 126 patients submitted to lymph node evaluation. The median number of lymph nodes removed was three (range: one to 48); the median number of positive lymph nodes was three (range: one to 18). Pathologically confirmed positive lymph nodes (pN1) were found in 33 (26%) patients.

Survival in all patients in the study

The median length of follow-up was 4.5 years (range: 5 days to 14.0 years); 64 (51%) patients were alive at the last follow-up. The median overall survival was 44 months; 1- and 5-year survival rates of 84% and 43%, respectively, were identified. Data on median overall survival stratified according to the various stages, including hazard ratios (HRs), are given in Table 2. None of the currently available staging systems were able to accurately stratify survival in this patient cohort (Fig. 1). Univariate analysis showed that the worsening of survival was statistically significant for the following variables: tumour size of >5 cm (HR 2.50, 95% CI 1.27–4.93); multiple tumours (HR 1.79, 95% CI 1.05–3.04); pN1 status (HR 3.14, 95% CI 1.83–5.38); presence of grade 4 disease (HR 3.72, 95% CI 1.74–7.95), and microvascular invasion (HR 1.87, 95% CI 1.12–3.09) (Table 3). Final stepwise multivariate analysis showed statistically significantly worse survival in patients with grade 4 disease (HR 7.84, 95% CI 3.35–18.35), pN1 disease (HR 2.93, 95% CI 1.64–5.21) and microvascular invasion (HR 1.84, 95% CI 1.06–3.21) (Table 3).

Survival according to T (N0M0) classification

Of the 126 patients in whom lymph nodes were evaluated, 93 (74%) were found to have pathologically confirmed node-negative disease. At the time of last follow-up, 57 (61%) of these patients were alive. Median overall survival in these patients was 79 months; rates of 1- and 5-year survival amounted to 92% and 57%, respectively. The various staging systems did not distribute T-stages equally. Data on median overall survival including HRs are given in Table 2. None of the currently available staging systems were able to accurately stratify survival in this sub-cohort. Upon univariate analysis, only the presence of grade 4 disease was correlated with poor survival (HR 4.23; $P = 0.004$) (Table 3). Given the small sample size of patients with pN0 disease and their lower mortality, multivariate analysis was not performed in this subset of patients.

Comparison of survival in pN0 and pN1 patients

The presence of positive lymph nodes (pN1) correlated with poor survival. The HR for having any positive lymph node was 3.14 (95% CI 1.50–5.40) ($P < 0.001$). Median overall survival in patients with pN1 disease was 20 months; 1- and 5-year survival rates amounted to 61% and 13%, respectively. Having three or more positive lymph nodes was associated with even worse survival ($P < 0.001$). An analysis of the impact of lymph node ratio (number of positive nodes/total number removed) on survival showed that a ratio of >0.1 correlated with poor survival (HR 1.34, 95% CI 1.20–1.50).

Levels of concordance and 95% CIs were calculated for the different staging systems and for the multivariable models (Fig. 2). Model 1 included a tumour size of >5 cm in addition to

Table 2 Cox proportional hazard ratios and overall median survival for various tumour–node–metastasis (TNM) staging systems

	TNM stage	*n* (%)	Median OS, months	HR (95% CI)	*P*-value
AJCC 7th edn[11]	I	33 (22%)	70	Referent	
	II	27 (18%)	90	0.95 (0.42–2.11)	0.895
	III	5 (3%)	Not reached	0.0 (0.0–2.10)	0.160
	IVa	61 (40%)	32	2.35 (1.26–4.37)	0.007
AJCC 6th edn[21a]	I	36 (31%)	70	Referent	
	II	20 (27%)	66	0.99 (0.43–2.23)	0.975
	IIIa	17 (15%)	41	1.33 (0.51–3.46)	0.552
	IIIb	11 (9%)	99	0.93 (0.31–2.81)	0.899
	IIIc	33 (28%)	22	3.31 (1.70–6.42)	<0.001
Okabayashi *et al.*[13a]	I	40 (34%)	79	Referent	
	II	20 (17%)	66	1.07 (0.47–2.43)	0.879
	IIIa	24 (21%)	81	1.46 (0.66–3.24)	0.346
	IIIb	33 (28%)	20	3.59 (1.87–6.88)	<0.001
Yamasaki[12]	I	1 (1%)	79	Referent	
	II	48 (41%)	66	–	–
	III	32 (27%)	81	1.23 (0.60–2.51)	0.570
	IVa	36 (30%)	20	3.17 (1.75–5.74)	<0.001

AJCC 7th edn T (N0M0) staging

T-stage	*n* (%)	Median OS, months	HR (95% CI)	*P*-value
T1	37 (29%)	70	1.00 (referent)	
T2a	14 (11%)	Not attained	0.39 (0.10–1.38)	0.145
T2b	26 (21%)	41	1.56 (0.65–3.75)	0.323
T3	8 (6%)	Not attained	0.0	0.182
T4	41 (33%)	66	1.6 (0.72–3.53)	0.251

[a]Missing staging information in nine patients.
AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; N0M0, node-negative and metastasis-negative disease; OS, overall survival.

AJCC 7th edition staging and reached a concordance of 0.66 (95% CI 0.58–0.74). Model 2 included tumour size of >5 cm, grade 4 disease, multiple tumours, periductal invasion, pN1 disease and microvascular invasion, and reached a concordance of 0.71 (95% CI 0.62–0.79).

Discussion

This study demonstrates that the current staging systems (the AJCC 6th edition, AJCC 7th edition, and those devised by Okabayashi *et al.*[13] and Yamasaki[12]) do not accurately stratify survival in this patient cohort. However, the univariate analysis of survival outcomes demonstrated that multiplicity of disease, size and vascular invasion were key prognostic factors for survival, as were angiolymphatic invasion, lymph node status and grade of tumour. Multivariate analysis demonstrated that only a resection margin of >5 cm, grade 4 disease, and lymph node status were significant factors. In this study, the median length of overall survival following surgical resection for ICC was 44 months, which is higher than survival times reported in other studies, despite the higher rate of major resection.

There were several differences in survival between this cohort and the cohort[15] used to propose the AJCC 7th edition, which may account for the survival differences observed. For example, the current study included only patients in whom lymph node status was evaluated, among whom the proportion of patients with positive-margin surgical resection was very small and in whom survival was notably higher and follow-up more extended in comparison with those in the cohort sourced from the SEER database.[14]

This study found that tumour size and grade 4 disease may play significant roles in the prognosis of ICC patients after surgical resection. The multivariable model, which included tumour size and grade in addition to variables in the AJCC 7th edition, achieved a concordance of 0.71.

Currently, lymph node disease in ICC patients is reported as either present or absent in all of the staging systems available. This study not only confirmed the presence of pN1 disease to be associated with poor survival, but further analysis suggested that increasing the lymph node ratio (positive lymph nodes/total number removed) correlated with worse survival. The prognostic

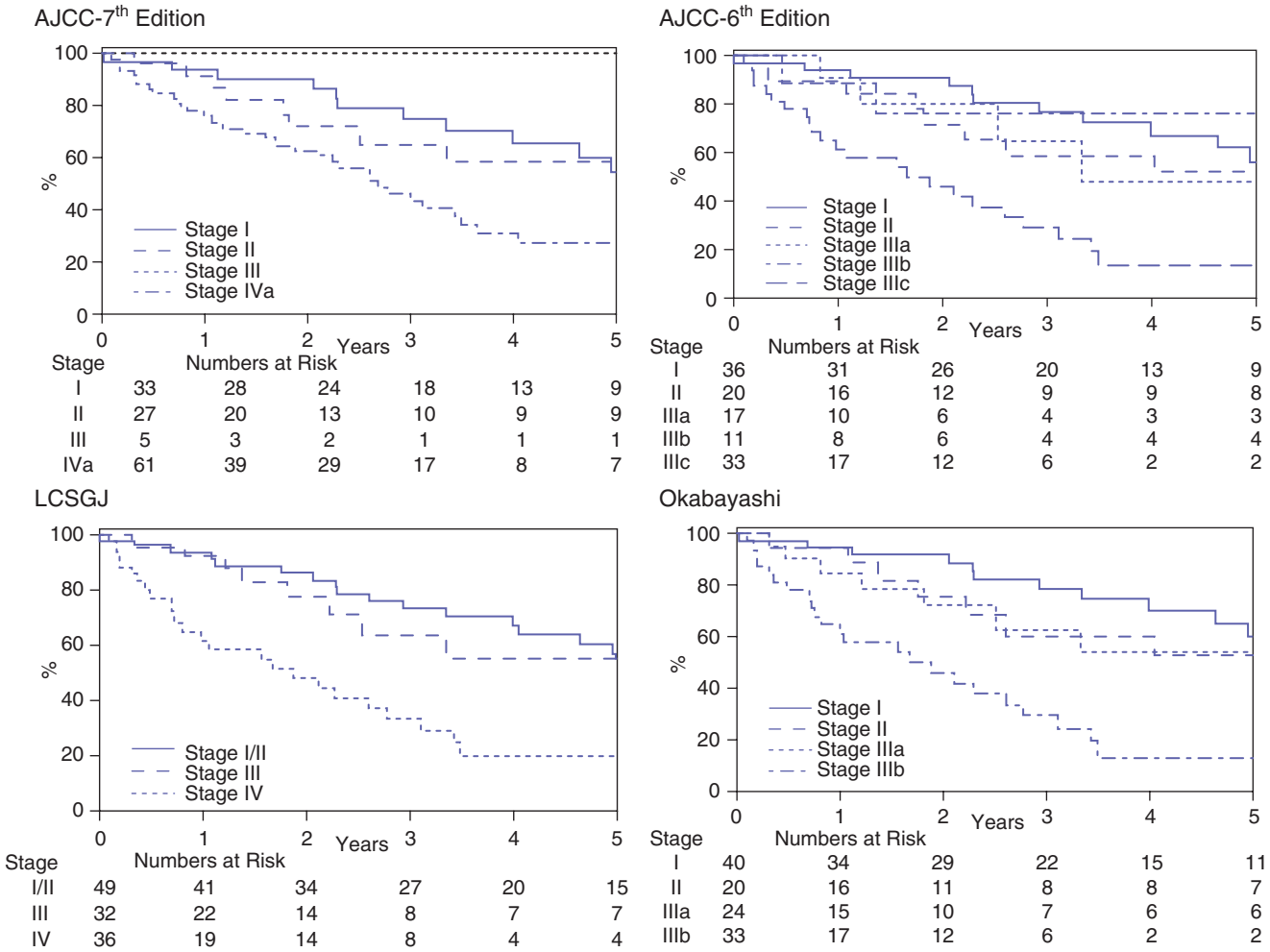

Figure 1 Kaplan–Meier survival plots comparing various staging systems. AJCC, American Joint Committee on Cancer; LCSGJ, Liver Cancer Study Group of Japan

importance of lymph node ratio to survival has been shown in one prior study, which reported that an increasing lymph node ratio was associated with a poorer prognosis.[21] However, a recent analysis based on data from the SEER database[14] reported that data on lymph node status were available for only 49% of patients submitted to surgery for ICC, and that a histological evaluation of lymph nodes was performed in only 14% and the median number of lymph nodes harvested was two.[21] Furthermore, there is no consensus on the optimal number of lymph nodes that should be harvested for accurate lymph node staging. Although the role of lymph node sampling is undetermined, these data suggest that routine lymph node evaluation is warranted in patients with ICC in order to elucidate the impact of lymph node status on prognosis.

In this study, resection margin status was an important determinant of prognosis in ICC patients. The current analysis showed that negative surgical margin status correlates with improved survival and similar findings have been reported in multiple prior studies.[7,10,22] However, the optimal margin width in patients with R0 resection remains undetermined. The present findings were corroborated by those of a recent study that reported a margin width of >5 mm in pN0 patients as an independent predictor of improved survival.[23] Efforts should be made to obtain a 5-mm negative surgical margin.

The present study has several limitations. Its retrospective design and the fact that it was conducted at a single tertiary care centre may have led to some degree of selection bias. The sample size, although relatively large for a single centre, may not have been sufficiently powered to accurately predict survival in various TNM staging models. Furthermore, the impact of chemotherapy was not assessed. Nonetheless, this is the first single-centre study from the USA to have evaluated the validity of the AJCC 7th edition staging system. Furthermore, only completely staged patients were included in the survival analysis and all histological subtypes were included. Given the high proportion of patients

Table 3 Univariate and multivariate hazard ratios for node-negative and metastasis-negative (N0M0) patients and all patients

Variables	N0M0 patients (*n* = 93)					All patients (*n* = 126)				
		n	Median survival, months	HR (95% CI)	*P*-value		*n*	Median survival, months	HR (95% CI)	*P*-value
Univariate analysis										
Tumour size of >5 cm	Yes	58	60	1.91 (0.87–4.20)	0.102	Yes	88	38	2.50 (1.27–4.93)	0.008
	No	35	99			No	38	99		
Grade 4 disease	Yes	6	14	4.23 (1.58–11.28)	0.004	Yes	10	6	3.72 (1.75–7.95)	<0.001
	No	87	81			No	116	49		
Periductal invasion	Yes	28	66	1.75 (0.85–3.61)	0.123	Yes	41	38	1.61 (0.96–2.69)	0.064
	No	65	84			No	85	60		
Direct invasion	Yes	11	70	0.85 (0.30–2.41)	0.762	Yes	18	43	1.21 (0.61–2.39)	0.582
	No	82	99			No	108	49		
Macrovascular invasion	Yes	9	49	1.36 (0.48–3.86)	0.561	Yes	11	44	1.32 (0.60–2.89)	0.491
	No	84	81			No	115	49		
Microvascular invasion	Yes	37	66	1.12 (0.57–2.17)	0.741	Yes	60	32	1.87 (1.13–3.09)	0.016
	No	56	79			No	66	70		
Multiple tumours	Yes	30	81	1.40 (0.67–2.92)	0.362	Yes	38	31	1.79 (1.05–3.04)	0.031
	No	63	79			No	88	57		
Positive lymph nodes	–	–	–	–	–	Yes	33	20	3.14 (1.83–5.39)	<0.001
						No	93	79		
Multivariate analysis										
Grade 4 disease						Yes	10	6	7.84 (3.35–18.35)	<0.001
						No	116	49		
Positive lymph nodes						Yes	33	20	2.93 (1.65–5.21)	<0.001
						No	93	79		
Microvascular invasion						Yes	60	32	1.85 (1.06–3.22)	0.030
						No	66	70		
Multiple tumours						Yes	38	31	1.68 (0.96–2.92)	0.067
						No	88	57		
Periductal invasion						Yes	41	38	1.53 (0.87–2.68)	0.136
						No	85	60		
Tumour size of >5 cm						Yes	88	38	1.51 (0.75–3.06)	0.248
						No	38	99		
Resection margin	–	–	–	–	–	R0	110	66	–	–
						Non-R0	16	25		
Margin width	–	–	–	–	–	>5 mm	70	99		<0.001
						<5 mm	56	38		

CI, confidence interval; HR, hazard ratio; N0M0, node-negative and metastasis-negative disease.

submitted to lymph node evaluation, it was feasible to study the impact of the number of positive lymph nodes on survival. The strengths of the study include the fact that all histopathological examinations were conducted by a single pathologist, which enabled the accurate staging of patients and a prolonged follow-up of 4.5 years.

To summarize, none of the available staging systems were able to accurately stratify survival in the current cohort. The Mayo Clinic staging model added a tumour size of >5 cm and the presence of grade 4 disease to the AJCC 7th edition model and improved concordance to only 0.71. Further studies are needed to test the validity of these findings. As none of the published studies show favourable groupings in terms of the various staging systems, multicentre studies from the USA that include completely staged patients may help to overcome this barrier. Furthermore, such multicentre trials will probably give sufficient power to

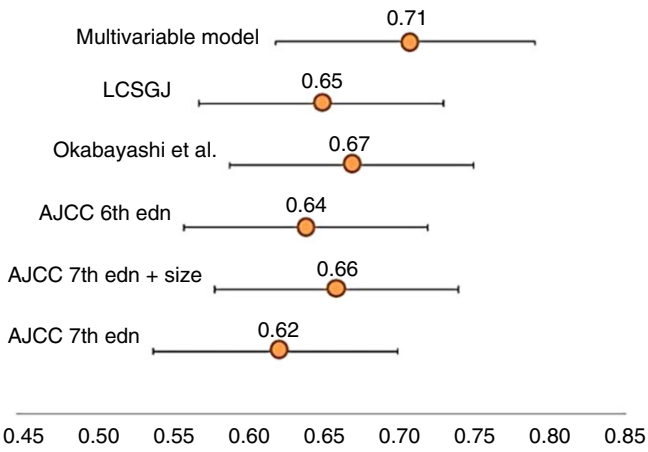

Figure 2 Comparative concordance values with confidence intervals for the various staging systems and the multivariable model. AJCC, American Joint Committee on Cancer; LCSGJ, Liver Cancer Study Group of Japan

support the development of a model that will accurately predict the survival of ICC patients in the USA.

Conflicts of interest

None declared.

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